REMARKS

Because the Advisory Action of August 12, 2010, indicates that the amendments and arguments in Applicants' response of July 26, 2010, were not entered, the identical claim amendments as well as arguments are again presented herein.

I. Status of the Claims

Upon entry of the present amendment, claims 17-42 and 50-63 are pending. Claims 35, 36, 41, 42, 56, and 57 are amended to clarify that SEQ ID NO:24 refers to the wild-type PE. Claim 50 is amended in accordance with the Examiner's suggestion.

II. Allowable Subject Matter

Applicants note with appreciation that the Examiner has indicated claims 17-34, 37-40, 50-55, and 61-63 are allowed.

III. Telephonic Interview

Applicants thank Examiners Dahle and Shukla for the telephonic interview of June 22, 2010. The rejection under 35 U.S.C. § 112, second paragraph, was discussed. Applicants note with appreciation the Examiner's indication during the interview that the claims are not rejected for lack of enablement. In the interest of properly responding to all the issues in the pending Office Action, Applicants respond to the rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement below.

IV. Claim Objection

The Examiner has objected to claims 50-57 based on the language of claim 50. Applicants do not agree with the Examiner. In the interest of expediting prosecution, however, Applicants have amended claim 50 in accordance with the Examiner's suggestion.

V. Claim Rejections

A. 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 35, 36, 41, 42, 56, and 57 as allegedly indefinite. In particular, the Examiner alleges that the characteristics of the recited PE variants are not known.

The test for definiteness under 35 U.S.C. 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification" (emphasis added). M.P.E.P. § 2173.02, *citing to Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Under 35 U.S.C. § 112, second paragraph, the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. M.P.E.P. § 2171. This requirement is objective and is evaluated in the context of whether the claim is definite, *i.e.*, whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art (emphasis added). *Id.* A fundamental principle contained in 35 U.S.C. § 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose. M.P.E.P. § 2173.01. As noted by the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought. *Id.* The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. M.P.E.P. § 2173.05(a).

In this case, at the time of the November 25, 2003, priority date of the present application, those of skill in the art readily recognized the *Pseudomonas* exotoxin A ("PE") variants recited in claims 35, 41, and 56, and referred to them by their so-called laboratory names. This is evidenced by a search of the academic literature on PubMed. For example, a search for the term "PE40" retrieves 195 results, 169 of which were published before November 2003.[1] Of the total number of references retrieved, 177 relate to the PE variant PE40

[1] The results of the PubMed search for PE40 is provided as Exhibit A with this response.

(highlighted) and 18 do not. Numerous publications cite to "PE40" in their titles, indicating this is the term used by those of skill in the art to identify this PE variant. The term "PE40" was coined in the laboratory of co-inventor Dr. Ira Pastan and published in the literature since 1987. Many of the retrieved publications include Dr. Pastan as co-author. It is also noted that numerous publications referencing "PE40" are published by laboratories independent of Dr. Pastan's, but that recognize and use this term, *e.g.*, in the title or abstract, to refer to a particular PE variant. *See, e.g.*, result numbers 1, 3, 5, 7-9, 12, 15-18, 20-21, 23, 25, 28-30, 32-33, 35, 38, 41, 43, 45-56, 58-60, 62-66, 68-69, 72, 73, 76-89, 91-93, 95, 97-100, 103-106, 113, 116-117, 119, 124, 126-127, 132, 136-137, 141, 143, 146, 148, 151, 158, 178, and 183. Clearly, those of skill in the art recognize the PE variant intended by the term PE40.

The PubMed search executed for the term "PE38" retrieved 195 results, about 100 of which were published before November 2003.[2] Of the total number of references retrieved, 159 relate to the PE variant PE38 and 36 do not. Numerous publications cite to "PE38" in their titles, indicating this is the term used by those of skill in the art to identify this PE variant. The term "PE38" was also coined in the laboratory of co-inventor Dr. Ira Pastan and published in the literature since 1992. Therefore, many of the retrieved publications include Dr. Pastan as co-author. It is also noted that numerous publications referencing "PE38" are published by laboratories independent of Dr. Pastan's, but that recognize and use this term, *e.g.*, in the title or abstract, to refer to a particular PE variant. *See, e.g.*, result numbers 1, 3, 6, 8-10, 12-13, 18-19, 21, 23-25, 27, 31-39, 43, 47, 49-50, 54, 58, 60-63, 65, 68-70, 73-75, 79-83, 87-89, 91, 93-94, 96-97, 99, 102-103, 106, 111-113, 115, 119-121, 123, 125, 137, 143-144, 149, and 155-156. Clearly, those of skill in the art also recognize the PE variant intended by the term PE38.

The PubMed search executed for the term "PE38QQR" retrieved 58 results, all of which relate to the PE variant recited in the claims.[3] Accordingly, those of skill in the art oftentimes have used the term PE38QQR to refer to a particular PE variant. PE38QQR has be discussed in the published academic literature since 1992.

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[2] The results of the PubMed search for PE38 is provided as Exhibit B with this response.
[3] The front pages of the results of the PubMed search for PE38QQR is provided as Exhibit C with this response.

Similarly, a PubMed search for the term "PE38KDEL" retrieved 86 results, 83 of which related to the PE variant.[4] PE38KDEL has been discussed in the scientific literature since 1993. Applicants also provide in Exhibit D the 12 results retrieved searching for the term "PE40KDEL." It is clear from the retrieved search results that those of skill recognize what is meant by the "KDEL" substitution at the C-terminal residues of a PE molecule, and that such a substitution can be made in either the PE38 or PE40 variants.

With respect to the PE variant PE4E, a PubMed search for this term retrieved 15 results, all of them relating to the PE variant.[5] The term "PE4E" was also coined in the laboratory of co-inventor Dr. Ira Pastan and published in the literature since 1992.

With respect to the PE variant PE35, a PubMed search for this term retrieved 26 results, 6 of them relating to the PE variant.[6] However, as discussed during the interview of June 22, the claims define the acronym "PE" as referring to *Pseudomonas* exotoxin, *e.g.*, in claims 34, 40 and 55. Therefore, in the context of the claims and the specification, it is clear that the PE35 recited in the claims is a *Pseudomonas* exotoxin variant, and not an antibody or a *Mycobacterium tuberculosis* antigen. In the context of PE variants, the term "PE35" was also coined in the laboratory of co-inventor Dr. Ira Pastan and published in the literature since 1996.

Consistent with the abundant number of references that refer to the names of Dr. Pastan's PE variants, the USPTO has also issued numerous patents with claims that recite these terms. Applicants provide with this response the claims issued in 23 patents, namely U.S. Patent Nos. 7,521,054; 7,368,110; 7,355,012; 7,129,332; 6,518,061; 6,287,562; 6,051,405; 6,011,002; 5,919,456; 5,889,157; 5,863,745; 5,854,044; 5,821,238; 5,705,163; 5,696,237; 5,635,599; 5,614,191; 5,608,039; 5,602,095; 5,512,658; 5,458,878; 5,206,353 and 5,082,927.[7]

Finally, although the terms of Dr. Pastan's PE variants were already well known to those of skill in the art and also recognized by the USPTO at the time of filing the present

[4] The results of the PubMed search for PE38KDEL is provided as Exhibit D with this response.
[5] The results of the PubMed search for PE4E is provided as Exhibit E with this response.
[6] The results of the PubMed search for PE35 is provided as Exhibit F with this response.

application, the specification also teaches the details of the construction of the PE variants, *e.g.*, in paragraphs [0157-0161], as discussed in the response submitted on January 4, 2010. The Examiner alleges that Applicants have attempted to incorporate subject matter of the mutated PE into the application. *See*, page 4 of the present Office Action. Applicants respectfully disagree. At the time of filing the present application, the PE variants were already well known in the art and recognized by those of skill by their names. Although it was sufficient to refer to them by name in the specification, in the interest of clarity, the specification teaches the details of their design and directs the reader to relevant supporting references.

With respect to the language in claims 35, 36, 41, 42, 56, and 57, which recites PE variants wherein the position corresponding to position 490 of SEQ ID NO:24 is substituted, Applicants understood the Examiner to request during the interview that the language in the claims clarify that SEQ ID NO:24 is the wild-type PE sequence. In response, Applicants have amended claims 35, 36, 41, 42, 56, and 57 clarify that SEQ ID NO:24 is wild-type PE.

For at least the foregoing reasons, the Examiner is requested to withdraw this rejection.

B. 35 U.S.C. § 112, First Paragraph: Enablement

Claims 35, 36, 41, 42, 56, and 57 are rejected under 35 U.S.C. 112, first paragraph, as allegedly not enabled. Applicants understand from the interview of June 22, 2010, that the Examiner does not object to the claims as allegedly not enabled.

In the interest of completely responding to the present Office Action, Applicants respectfully traverse the enablement rejection.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ 1510, 1513 (Fed. Cir. 1993). As set forth in M.P.E.P. § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether... it is undue." Further, the "fact that experimentation may be complex does not

[7] The issued claims in the listed patents are provided as Exhibit G.

necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971). Furthermore, a patent need not teach, and preferably omits, what is well known in the art. *See, In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). *See also*, M.P.E.P. § 2164.01.

Here, the Examiner alleges that Applicants are attempting to incorporate essential material in to the specification by reference. *See*, pages 5-6 of the present Office Action. Applicants respectfully disagree. As demonstrated in the PubMed search results for Dr. Pastan's named PE variants, those of skill readily recognized the PE variants recited in the claims by name years before the filing of the present application. Because the PE variants were already well known in the art, in accordance with M.P.E.P. § 2164.01, it was not necessary to teach their design and construction in paragraphs [0157-0161]. However, in the interest of clarity, the specification provides information that teaches those of skill how to make the different PE variants starting from the native PE sequence (SEQ ID NO:24).

The Examiner acknowledges that the specification is enabled for the improved anti-CD22 antibodies that are the inventive principle of the present invention. Claims 35, 36, 41, 42, 56 and 57 are directed to chimeric molecules created by linking a known PE variant to the antibodies that are the inventive principle of the present claims. Immunotoxin technologies were well known at the time of filing the present application and immunotoxins comprising the recited PE variants were also well known at the time of filing the present application.

For at least the foregoing, those of skill in the art could readily make and use chimeric molecules comprising the improved anti-CD22 antibodies conjugated or linked to a well known and publicly described PE variant without undue experimentation and with a reasonable expectation of success. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 20-1430.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments (Exhibits A-G)
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